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Selected Topics: Toxicology

CIMETIDINE-INDUCED DYSTONIC REACTION

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Abstract—A 39-year-old woman presented to the Emergency Department complaining of nausea and vomiting. The patient was given intravenous cimetidine for epigastric pain and subsequently developed a dystonic reaction. Administration of cimetidine, an H2 receptor antagonist, is an uncommon cause of dystonic reaction. We discuss the pathophysiology, diagnosis, and treatment. © 2001 Elsevier Science Inc.

Keywords—cimetidine; dystonic reaction; H-2 blockers

INTRODUCTION

Dystonic reactions are typically described as sustained abnormal postures and disruptions of movement resulting from alterations in muscle tone. The most common manifestations of dystonia are bizarre muscle spasms of the facial, neck, and tongue, causing oculogyric crises, torticollis, swallowing or chewing difficulties, and masseter spasms, respectively. Younger patients are at higher risk than are older ones (1). Acute dystonia is a dramatic form of extrapyramidal side effects of antipsychotic medications (1). High potency antipsychotics (haloperidol and fluphenazine) and antiemetics (prochlorperazine and metoclopramide) are traditionally the most common drugs implicated in dystonic reactions (1,2). Cimetidine is not a common cause of dystonic reaction, however, there are a handful of reports implicating type 2 histamine antagonists as a cause of dystonia and other extrapyramidal syndromes, but there is no agreement on the pathophysiology of this reaction (3–8). We present a case of dystonic reaction induced by cimetidine given intravenously (i.v.) and a brief discussion of dystonic reactions, proposed pathophysiologic mechanisms, and treatment of this disorder.

CASE PRESENTATION

A 39-year-old woman presented via ambulance to the Emergency Department (ED) with a chief complaint of nausea and vomiting with epigastric pain for the last 3 days. The patient had not taken her antiepileptic medication for 5 days and had a seizure 1 h prior to arrival. The patient had presented to the ED 1 week prior for the same complaints.

During her previous visit to the ED, the patient was given i.v. prochlorperazine for the multiple episodes of nausea and emesis. She had a dystonic reaction described as "tip smacking," or masseter spasms, and an oculogyric crisis within 5–7 min of administration of prochlorperazine. The patient was given 50 mg diphenhydramine intramuscularly, and the symptoms resolved completely within 5 min. She was admitted to the hospital for intractable vomiting, restarted on her seizure medications, and subsequently discharged.

Since the dystonic reaction of the prior week, the patient denied any similar reactions, psychiatric history,

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of any use of antipsychotic medication. She did not use antiemetics before coming to the ED. The patient also denied any illicit drug or alcohol use, but admitted to smoking one pack of cigarettes per day. Her medications included an albuterol inhaler for asthma, alprazolam for GI anxiety, and phenytoin for epilepsy.

Physical examination revealed a well-developed woman in no acute distress. Vital signs were blood pressure of 140/91 mm Hg, pulse of 94 beats/min, respiratory rate of 18 breaths/min, and an oral temperature of 36.5°C (97.7°F). The physical examination was unremarkable except for mild epigastric tenderness with no guarding or rebound tenderness. The rectal examination was hemoccult negative with brown stool and good sphincter tone.

An i.v. line was placed and blood work (CBC with differential, SMA 7, phenytoin level, amylase, and lipase) was sent to the laboratory. Intravenous normal saline and i.v. cimetidine 300 mg were ordered.

Within 5 min of administering cimetidine 300 mg i.v., the patient experienced a dystonic reaction similar to the reaction she had when prochlorperazine was administered. The patient initially had masseter spasm with mild lip smacking and then experienced an oculogyric crisis. She also experienced a mild neck spasm during the dystonic reaction.

The i.v. cimetidine was immediately stopped, and the patient was administered diphenhydramine 50 mg i.v. along with 2 mg of lorazepam i.v., which relieved her dystonic reaction within 5 min of administration. Steps were taken to ascertain whether an error was made in administration of another medication. There was a written order for cimetidine. Medication in our ED is dispensed through the Pyxis system, which takes into account a patient's allergies and delivers medication from computerized and labeled slots. All activity is recorded and can be reviewed. This is to prevent incorrect or possibly harmful medication being given to a patient. After extensive review by the nurse, resident physician, and the attending physician, we concluded that the patient did indeed receive cimetidine.

The laboratory data revealed no significant changes compared to the results of 1 week ago. After the resolution of the dystonic reaction, she remained asymptomatic during the hospital stay. The patient was loaded with phenytoin, and was discharged 8 hours later after tolerating oral fluids. She was given diphenhydramine to continue after discharge.

DISCUSSION

Dystonic reactions are adverse extrapyramidal side effects that can occur shortly after the initiation of neuroleptic drug therapy and may occur with a wide variety of medications. Acute dystonic reactions are characterized by intermittent spasmodic or sustained involuntary contractions of muscles in the face, neck, trunk, pelvis, and extremities. In adults, the head and neck muscles are the most frequently involved (1). Although dystonic reactions are rarely life threatening, they are very uncomfortable and often produce significant anxiety and distress for patients.

Drugs that alter the dopaminergic-cholinergic balance in the nigro-striatal pathway (in the basal ganglia) have been implicated in producing extrapyramidal side effects. Most drugs produce dystonic reactions by nigrostriatal D2-dopamine receptor blockade, which leads to an excess of striatal cholinergic output. It remains unclear if dystonia is caused by the relative relationship of the two receptors or by an excess or lack of one of the components (9). The drugs often implicated in causing dystonic reactions are high potency D2-receptor antagonists, including neuroleptic agents; antiemetics, such as prochlorperazine and trimethobenzamide; and the antireflux agent, metoclopramide (2,9,10). Any agent that balances dopamine blockade with M1-muscarinic receptor blockade is less likely to produce a dystonic reaction.

van't Groenewout et al., using selective microinjection to different areas of the basal ganglia, demonstrated in a rat model that the antihistamine properties of both diphenhydramine (H1) and cimetidine (H2) can have antidystonic effects (11). In the same paper they reported that the anticholinergic medicine had no effect on dystonia. Davis et al. reported a case of a cranial dystonia caused by ranitidine and suggested that the location of the anticholinergic or dopaminergic effects of the drug may play a role in causing dystonia (6).

Dystonic reactions are more likely to occur with increasing dosage and frequency, but may occur after a single dose. Goldfrank et al. believed that dystonic reactions are often "idiosyncratic" (12). These reactions usually occur within 24–72 h and may even occur as late as 5 days after the first dose or after an increase in the maintenance dose.

Cimetidine is a histamine type-2 receptor antagonist used in the treatment of gastric and duodenal ulcers and is considered the drug of choice for the treatment of an uncomplicated peptic ulcer (13). The drug produces no known alterations of the central dopaminergic pathways (11). Central nervous system reactions, such as coarse postural and action tremors, and involuntary motor symptoms, including dystonia, have been reported with cimetidine therapy (7,8,10). Side effects are typically reversible on discontinuation of the medication. Predisposing factors for such reactions include older age, renal and hepatic impairment, higher dosages, pre-existing psychiatric illness, and simultaneous treatment with psy-

chotropic medication (10). Our patient had none of these characteristics, and the alprazolam that she was taking might be considered as protective against a dystonic reaction.

In our case the dystonic reaction was very likely caused by the cimetidine. It was the only medication that was given because the patient was unable to tolerate anything by mouth. It is unlikely that the patient's previous dystonic reaction to prochlorperazine 1 week earlier was related because of the asymptomatic period between the episodes and because of the temporal relationship to cimetidine.

Treatment of dystonic reactions involves discontinuing the suspected offending drug and giving an anticholinergic agent to suppress the increased cholinergic output. Securing the airway may be necessary with laryngeal and pharyngeal dystonic reactions when respiratory compromise occurs. Usually pharmacological treatment, such as diphenhydramine HCl or benztropine mesylate, is needed to resolve the reaction. Other medications used in the treatment of dystonic reaction include trihexyphenidyl, biperiden, or benzodiazepines, such as diazepam or lorazepam (12).

Despite dystonic reactions resolving rapidly after a single dose of anticholinergic medicine, the suspected medicine must be discontinued, and anticholinergics must be continued for 48–72 h to prevent a relapse (14).

SUMMARY

We present a case of a dystonic reaction associated with cimetidine administration. The mechanism of dystonic reactions is most commonly attributed to a disruption of the dopaminergic-cholinergic neuropathways in the basal ganglia. The exact neurochemical problem and location in the brain have yet to be identified. Though not common, cimetidine must be considered as a potential cause of dystonia. Because cimetidine has been approved for over-the-counter use, it is possible that more dystonic reactions caused by this drug will occur.

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